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Effects of HMG-CoA reductase inhibitors in hypercholesterolemic patients on hemodialysis

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Effects of HMG-CoA reductase inhibitors in hypercholesterolemic patients on hemodialysis. The efficacy of lovastatin and simvastatin, competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase, was investigated in 40 hemodialysis (HD) patients displaying hypercholesterolemia and moderate hypertriglyceridemia (selection of 40 patients required screening of 700 hemodialysis patients). After a four-week placebo period, lovastatin or simvastatin was administered to two groups of 20 patients in increasing doses over a period of three months. Thirty-six patients completed the study. Lovastatin (1st month 20 mg; 2nd and 3rd months 40 mg day^{-1}) and simvastatin (1st month 10 mg, 2nd month 20 mg and 3rd month 40 mg day^{-1}) reduced total serum cholesterol from 280.3 ± 9.4 to 213.0 ± 6.7 (−24%) and 295.0 ± 12.2 to 202.3 ± 8.9 mg/dl (−31.4%), LDL cholesterol from 161.9 ± 10.7 to 112.1 ± 7.9 (−30.8%) and 181.8 ± 14.7 to 107.4 ± 8.1 mg/dl (−40.9%), as well as apolipoprotein B (apo B) from 116.0 ± 6.6 to 83.3 ± 3.7 (−28.2%) and 134.4 ± 8.2 to 84.1 ± 5.3 mg/dl (−37.4%), respectively. Furthermore, the ratio of LDL apo B/LDL cholesterol increased significantly (0.63 ± 0.02 vs. 0.71 ± 0.05 and 0.63 ± 0.02 vs. 0.66 ± 0.02, respectively). Another remarkable effect was the reduction of cholesterol concentration in VLDL (72.4 ± 8.9 vs. 47.3 ± 6.8 [lovastatin] and 78.3 ± 11.1 vs. 50.7 ± 8.8 mg/dl [simvastatin], respectively). Therefore, the ratio of triglycerides/cholesterol in VLDL increased (3.2 ± 0.2 vs. 3.8 ± 0.3 and 3.2 ± 0.2 vs. 4.0 ± 0.2, respectively), indicating VLDL formation poor in cholesterol and rich in triglycerides. The main difference between the two drugs was that only simvastatin significantly reduced triglycerides but increased HDL cholesterol and apolipoprotein A-1. Although one patient developed a moderate increase in hepatic transaminases, the other 35 patients had no notable side effects. Measurement of simvastatin plasma levels 13.4 hours after drug administration showed plasma values between 4 and 45 ng/ml (in controls not detectable after 12 hr). At present, it appears that there are only a few selected patients with high serum cholesterol level among all HD patients who could be candidates for the treatment with HMG-CoA reductase inhibitors.

In patients with chronic renal failure there is current debate as to whether cardiovascular disease is accelerated or not [1–8]. The pattern of dyslipidemia in dialysis patients include those with mild hypertriglyceridemia and a decreased concentration of high density lipoprotein [9]. This group represents the major form of dyslipidemia. Although the reduction of plasma lipoproteins may diminish the risk of atherosclerosis [10, 11], the contribution of hypertriglyceridemia to coronary heart disease is conjectural. Therefore, it is also unclear whether this form of dyslipidemia should specifically be treated [reviewed in 12] and certainly no rationale exists to induce LDL receptors in these patients. On the other hand, Nestel, Fidge and Tan [13] and Minamisono and coworkers [14] described a group of HD patients with a predominant increase in lipoprotein remnants, cholesterol-enriched catabolic products of chylomicrons and VLDL. Furthermore, a few HD patients also exhibit increased levels of LDL cholesterol, among them very few patients with a familiar history of hypercholesterolemia.

Beside the uncertainty of treatment, several clinical problems emerge when trying to influence dyslipidemia with currently available substances. Primarily, the drugs that have been tested for lipid lowering in chronic renal failure are fibric acids. Accumulation and severe side effects, such as muscle toxicity and rhabdomyloysis [15, 16] have been reported. Although, effective when used in adequate dosage [17] several authors do not recommend fibric acid derivatives in patients with chronic and end-stage renal failure [reviewed in 18]. Other substances such as L-carnitine, low-molecular weight heparin and omega-3-polyunsaturated fatty acids have been demonstrated to be effective in lowering triglyceride and/or cholesterol in some studies, but many results are contradictory [19–21].

To investigate the effects of HMG-CoA reductase inhibitors in chronic renal failure we selected an unusual group of patients with predominant elevations of cholesterol in VLDL and LDL. We further studied the tolerance of lovastatin and simvastatin in this group of patients undergoing regular hemodialysis treatment.

Methods

Subjects

Forty patients with end-stage renal disease, who were enrolled in this study were on thrice weekly hemodialysis treatment since 5.8 ± 1.4 years (range 0.5 to 23 years); 36 patients completed the study. About 700 patients were screened in order to obtain the required number of patients who met the inclusion criteria and volonteered to enter the trial. The inclusion criteria were serum values for cholesterol > 260 mg/dl. Most of these patients displayed moderate hypertriglyceridemia. Patients with plasma triglyceride levels higher than 500 mg/dl were excluded. Twenty-three out of 36 patients had LDL cholesterol higher than 155 mg/dl. In the remaining 13 patients high levels of cholesterol in VLDL were responsible for the elevation of total cholesterol, required to fulfill the inclusion criteria. End-stage renal failure was due to chronic glomerulonephritis (12), inter-

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stitial nephritis (9), small kidneys of unknown origin (7), polycystic kidney degeneration (5), hypertension (4), rapid progressive glomerulonephritis (1), Morbus Bourneville-Pringle (1) and eclampsia (1). Excluded were patients with diabetes mellitus, secondary hyperparathyroidism, unstable angina pectoris, recent myocardial infarction, or congestive heart failure. None had thyroid or hepatic disease except one patient of the lovastatin group, who had a history of nonA-nonB hepatitis with intermittent elevation of transaminases in the past. Therefore, exclusion criteria did not allow to study old and multimorbid individuals with poor prognosis as well as diabetic patients with triglycerides > 500 mg/dl and elevated VLDL cholesterol. No patient was taking other specific hypolipidemic drugs. Eighteen patients in the lovastatin group as well as eighteen treated with simvastatin completed the trial and data could be obtained for evaluation.

Study design

Patients were subdivided into two groups consisting of 20 patients each. Patients of group I were treated with lovastatin and consisted of 11 females and 9 males (mean age 53.2 ± 2.7, range 34 to 70 years). After one month placebo baseline period, therapy was started with 20 mg lovastatin day^{-1} for one month, followed by 40 mg day^{-1} for another two months. Patients of group II were treated with simvastatin and consisted of 11 females and 9 males (mean age 55.6 ± 2.4, range 36 to 69 years). Simvastatin was given in a dosage of 10 mg day^{-1} during the first month, followed by 20 mg for another month and 40 mg for a third month. Tablets of lovastatin and simvastatin were supplied by Merck Sharp & Dohme (Munich, Germany). Both HMG-CoA reductase inhibitors were given as a single daily dose in the evening. During the study the patients were advised not to change their dietary habits. The current medication consisting mainly of antihypertensive medication and phosphate binders was also not changed. The patients were interviewed about any side effects of the medication, such as anorexia, nausea, vomiting, abdominal pain, allergic reactions, muscle cramps, myalgias. Special effort was undertaken to ensure compliance in those patients. The study was carried out according to the principles of the Declaration of Helsinki. All patients gave their informed consent before entering the study and the protocol for this study was approved by the appropriate institutional review board.

Sampling procedure

Blood samples were collected in tubes without any anticoagulant. All patients were studied after an overnight fast of at least 12-hours immediately before the start of hemodialysis at the beginning of the study and in monthly intervals. The blood samples were centrifuged within 30 minutes of collection. All measurements for lipoprotein parameters were performed in fresh serum. Routine hematologic and biochemical assessment including a full and differential blood count, creatinine, urea, sodium, potassium, phosphate, calcium, total bilirubin, blood glucose, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase (CK), gamma-glutamyltranspeptidase and lactate dehydrogenase were carried out before the study, as well as in monthly intervals and four weeks after completion of the study. EDTA-plasma was obtained at the end of the third month in simvastatin treated patients for determination of simvastatin (hydroxy-acid-form) plasma levels [22].

Lipid determination

Cholesterol and triglycerides were determined enzymatically using Boehringer Mannheim reagents (Cholesterol 704121, Triglyceride 704113). Apolipoproteins A-1 and B were determined by kinetic nephelometry using comercial kits and the "Array" nephelometer, both from Beckman (Palo Alto, California, USA). As a reference material, lyophilized control serum, in which the lipoproteins have been protected from denaturation by addition of saccharose before lyophilization [23], was used.

Lipoprotein separation

An aliquot of serum was subjected to preparative ultracentrifugation as described in the *Manual of Laboratory Operations* of the Lipid Research Clinics Program [24]. Modifications were performed as follows: very low density lipoproteins (VLDL) were isolated in a Kontron ultracentrifuge (Rotor No. TFT 45.6, in tubes of 1 cm diameter, volume 1.5 ml). Eight tenths ml of serum was pipetted into the tube, the weight of the tube was recorded and 0.2 ml of 0.9% NaCl solution was layered above the serum. Centrifugation was performed for exactly 18 hours at 30.000 rpm at 10°C. After centrifugation the floated VLDL-fraction was aspirated by a 1 ml syringe until the supernatant was completely clear. The volume was reconstituted to the original weight with 0.9% saline. The concentration of VLDL lipids was calculated by the difference between the concentrations of the different lipids in the serum and in the d = 1006 infranatant. The lipid composition of VLDL in the aspirated specimen was determined directly. The concentration of LDL-lipids was determined by the difference between VLDL-free serum, obtained after ultracentrifugation, and the supernatant of this fraction after precipitation of LDL by phosphotunctic acid/$MgCl_2$. In addition to ultracentrifugation, HDL cholesterol was determined by precipitation from whole serum by the same procedure. All lipid determinations of the same sample were performed sequentially on a Hitachi 704-analyzer. The coefficient of variation for cholesterol and triglyceride as well as the determination of LDL varied between 1 and 3%. This low interassay coefficient of variation could not be obtained by other technology used for lipoprotein quantation. Therefore, the discribed technology was selected for the present study.

Statistical analysis

The results are expressed as means ± SEM. Statistical analysis was performed by Student *t*-test for paired and unpaired observations. *P* values less than 0.05 were considered to be significant.

Results

The effects of sequentially increasing doses of lovastatin and simvastatin on serum lipids and lipoproteins are shown in Tables 1 and 2. Total serum cholesterol decreased by 21.3 ± 2.6% (mean ± SEM) after one month on 20 mg of lovastatin day^{-1} and by 23.9 ± 2.9% after another two months on 40 mg day^{-1} ($P < 0.001$). An even more pronounced effect could be observed after treatment with 40 mg of simvastatin (Table 2). Since the tubes have been layered with 0.9% sodium chloride (d

Table 1. Effect of increasing doses of lovastatin on serum cholesterol, triglycerides and their distribution in VLDL, LDL and HDL in 18 HD patients

	Placebo	20 mg	40 mg
Cholesterol	280.3 ± 9.4	220.7 ± 7.5[b]	213.0 ± 6.7[b]
VLDL	72.4 ± 8.9	55.6 ± 7.4[a]	47.3 ± 6.8[a]
LDL	161.9 ± 10.7	119.5 ± 6.7[b]	112.1 ± 7.9[b]
HDL	44.6 ± 2.6	43.9 ± 2.2	44.3 ± 1.6
Triglyceride	329.6 ± 35.6	305.1 ± 37.0	311.5 ± 49.9
VLDL	234.0 ± 35.2	224.8 ± 35.6	218.1 ± 46.7
LDL	59.1 ± 3.7	52.1 ± 3.9	52.3 ± 3.9
HDL	30.5 ± 2.8	28.8 ± 3.1	34.5 ± 3.6

The last dose (40 mg) was given over a period of two months.
Data are given in mg/dl as mean ± SEM.
[a] $P < 0.01$
[b] $P < 0.001$

Table 2. Effect of increasing doses of simvastatin on serum cholesterol, triglycerides and their distribution in VLDL, LDL and HDL in 18 HD patients

	Placebo	10 mg	20 mg	40 mg
Cholesterol	295.0 ± 12.2	225.3 ± 10.1[c]	204.3 ± 8.9[c]	202.3 ± 8.9[c]
VLDL	78.3 ± 11.1	59.9 ± 9.5[b]	48.3 ± 8.4[b]	50.7 ± 8.8[b]
LDL	181.8 ± 14.7	124.9 ± 8.5[c]	115.7 ± 8.3[c]	107.4 ± 8.1[c]
HDL	34.9 ± 2.7	40.6 ± 2.9[a]	40.3 ± 2.4[a]	44.2 ± 3.5[a]
Triglyceride	333.6 ± 42.7	304.0 ± 48.5[a]	258.5 ± 41.8[a]	269.9 ± 42.8[a]
VLDL	240.8 ± 42.2	214.5 ± 42.8	191.5 ± 41.3	203.9 ± 41.3
LDL	65.8 ± 5.3	48.8 ± 3.7[c]	44.3 ± 3.2[c]	43.1 ± 4.3[b]
HDL	27.0 ± 4.3	24.0 ± 11.8	22.7 ± 2.0	22.9 ± 2.0

Each dose was given over a period of one month.
Data are given in mg/dl as mean ± SEM.
[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$

= 1.006 g/ml) only lipoproteins exhibiting a hydrated density of less than 1.006 were floating. Therefore the 1.006 infranate contained IDL and LDL. Changes in total serum cholesterol were paralleled by reductions in LDL cholesterol, total serum apo B and apo B in LDL. LDL cholesterol fell by 24.1 ± 3.1% and 30.8 ± 4.2% on doses of 20 and 40 mg of lovastatin and by 31.4 ± 2.9%, 36.4 ± 2.4% and 40.9 ± 3.9% on doses of 10, 20 and 40 mg day^{-1} of simvastatin ($P < 0.001$ for both drugs).

Apo B levels are usually normal or subnormal in HD patients. Normal values of our laboratory are in the range of 90 to 130 mg/dl. Apo B was reduced significantly from 116.3 ± 6.6 to 83.3 ± 3.7 mg/dl (placebo vs. 40 mg day^{-1} lovastatin; $P < 0.01$) and from 134.4 ± 8.2 to 84.1 ± 5.3 mg/dl (placebo vs. 40 mg day^{-1} simvastatin; $P < 0.01$). Apo B in LDL fell by 26.0 ± 3.8% and 40.3 ± 4.1%, respectively (Fig. 1). Furthermore, a statistically significant rise of the ratio of LDL apo B/LDL cholesterol from 0.63 ± 0.02 to 0.71 ± 0.05 was noted during lovastatin and from 0.63 ± 0.02 to 0.66 ± 0.02 during simvastatin treatment (Fig. 2). Serum concentrations of HDL cholesterol were not altered in lovastatin treated patients but increased significantly during the third month of treatment with simvastatin (26.6 ± 2.4%; $P < 0.05$). However, both groups of patients differed significantly by their baseline (placebo) HDL cholesterol ($P < 0.05$). Therefore, the so-called atherogenic index, the ratio of LDL/HDL cholesterol decreased from 3.6 ± 0.3 to 2.5 ± 0.2 during lovastatin and

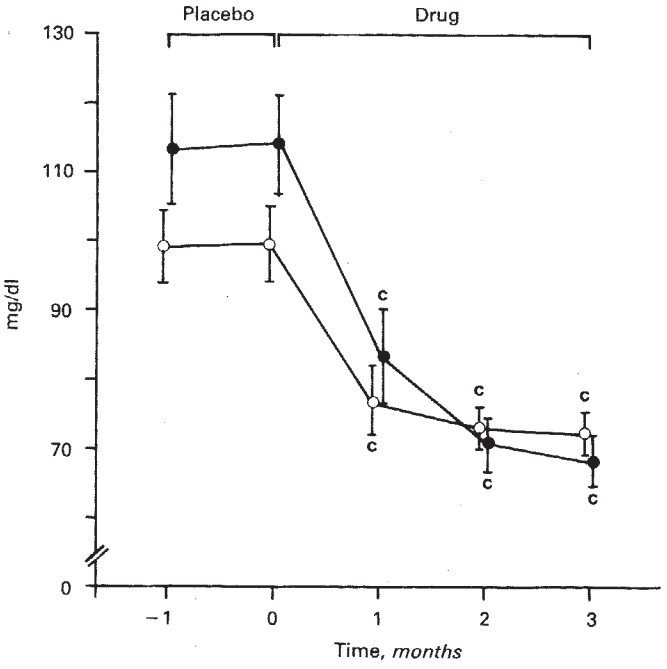

Fig. 1. *The influence of increasing doses of lovastatin (open circles) and simvastatin (solid circles) on apo B concentration in LDL in HD patients.* Data represent the mean ± SEM from 36 patients. c = $P < 0.001$.

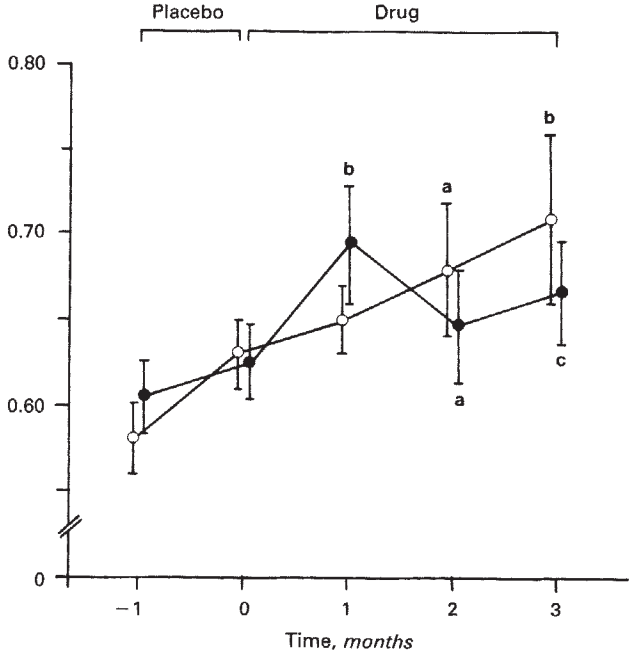

Fig. 2. *The influence of increasing doses of lovastatin (open circles) and simvastatin (solid circles) on the ratio of apo B to cholesterol in LDL in HD patients.* Data represent the mean ± SEM from 36 patients. a = $P < 0.05$, b = $P < 0.01$, c = $P < 0.001$.

from 5.9 ± 0.8 to 2.6 ± 0.2 during simvastatin therapy (Fig. 3). Consequently, serum values of apo A-1 remained constant during lovastatin 136.2 ± 5.0 vs. 135.3 ± 3.7 mg/dl) and

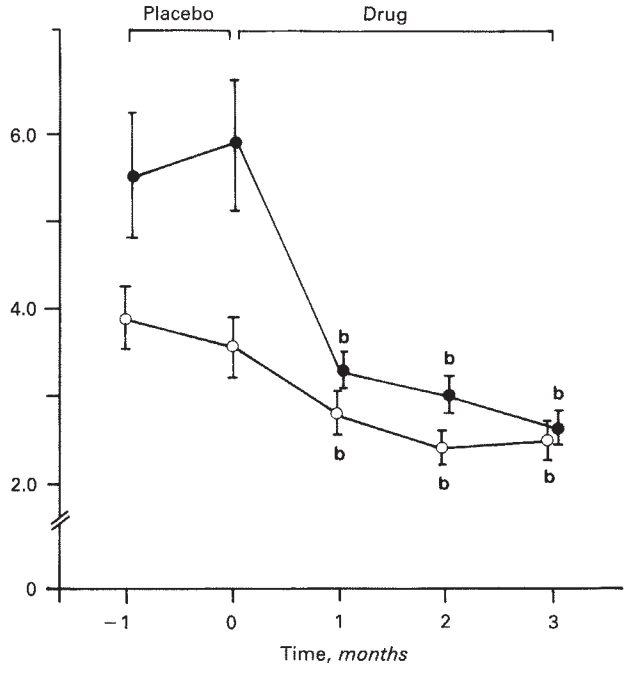

Fig. 3. *The influence of increasing doses of lovastatin (open circles) and simvastatin (solid circles) on the ratio of LDL cholesterol to HDL cholesterol in HD patients.* Data represent the mean ± SEM from 36 patients. b = $P < 0.01$.

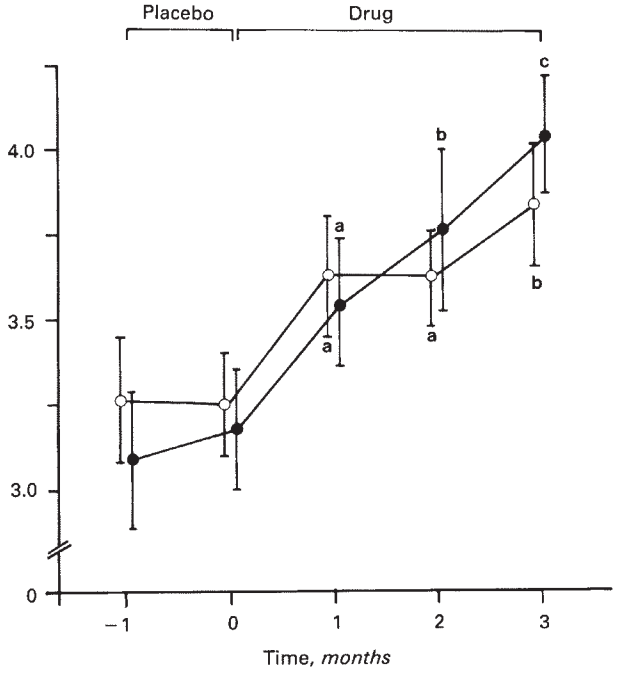

Fig. 4. *The influence of increasing doses of lovastatin (open circles) and simvastatin (solid circles) on the ratio of triglyceride to cholesterol in VLDL in HD patients.* VLDL-triglyceride/cholesterol for this figure was measured in VLDL isolated at d > 1.006 g/liter. Data represent the mean ± SEM from 36 patients. a = $P < 0.05$, b = $P < 0.01$, c = $P < 0.001$.

increased after the third month of simvastatin therapy (121.4 ± 6.1 vs. 145.9 ± 9.1 mg/dl; $P < 0.01$).

A pronounced lowering of cholesterol was observed in VLDL during three months of treatment with the two HMG-CoA reductase inhibitors (34.7 ± 5.3% and 35.2 ± 7.0%, respectively). Therefore, the ratio of triglycerides/cholesterol in VLDL increased significantly (3.25 ± 0.15 vs. 3.84 ± 0.18 and 3.18 ± 0.18 vs. 4.05 ± 0.18, respectively; Fig. 4).

Serum triglyceride metabolism is depicted in Tables 1 and 2. The SEM values for total and VLDL triglycerides in the Tables are higher compared to the other lipoprotein values. Six patients of group II (simvastatin) did not show any effect on total and VLDL triglycerides. Nevertheless, an overall significant reduction of total triglyceride was achieved by simvastatin (−21.3%; $P < 0.05$) and to a minor extent by lovastatin (−5.5%, NS). The reduction of LDL triglycerides was most evident after treatment with simvastatin (−34.5%; $P < 0.01$), whereas lovastatin reduced triglycerides in LDL by 18.5% (NS). Therefore, the ratio of triglycerides/cholesterol in LDL increased from 0.38 ± 0.02 to 0.51 ± 0.06 in the lovastatin group ($P < 0.01$), but remained stable during treatment with simvastatin (0.41 ± 0.03 vs. 0.42 ± 0.03; Fig. 5).

Adverse effects

No major side effects in both study trials occurred. For purpose of safety, all minor side effects are reported. Clinical chemistry parameters were evaluated in monthly intervals. There were no differences between placebo and lovastatin or placebo and simvastatin treated patients with respect to alanine aminotransferase, asparte aminotransferase, alkaline phosphatase, total bilirubin, creatine kinase, creatinine and urea. There were four drop outs. One patient underwent kidney transplantation during the third month of therapy. Another patient was withdrawn from the study due to non-compliance to medication. The third patient decided to leave the protocol due to gastrointestinal disturbances and obstipation during the placebo period. The fourth patient had to undergo aortic valve replacement after completion of the first month of active treatment. In all but one patient, liver enzymes remained whithin normal limits. The patient with a history of nonA-nonB hepatitis showed gradually increasing values of alanine aminotransferase and aspartate aminotransferase (third month: 190 and 53 U/liter, respectively). This elevation was completely reversed two weeks after withdrawal of lovastatin. There was no patient who experienced a continuous rise in creatine kinase above normal. There were single peak values of creatine kinase in four patients (73, 130, 134 and 138 U/liter, respectively; normal values 0 to 70 U/liter) during the study. Enhanced muscular activity in the dialysis interval or muscle cramps, as a possible cause for CK-elevation, were not reported by the patients before measurement. Two other patients had increased CK-values before the study, which decreased (322 vs. 169 U/liter) or moderately increased (101 vs. 179 U/liter) during the active treatment period. In all patients no muscular symptoms were reported. One patient developed severe pruritus and discontinued treatment one week before completing three months of treatment. Blood was obtained for determination of lipoproteins and serum chemistry and the values were taken as a final sample. This patient experienced a slight but not sustained release of the pruritus after discontinuation of therapy

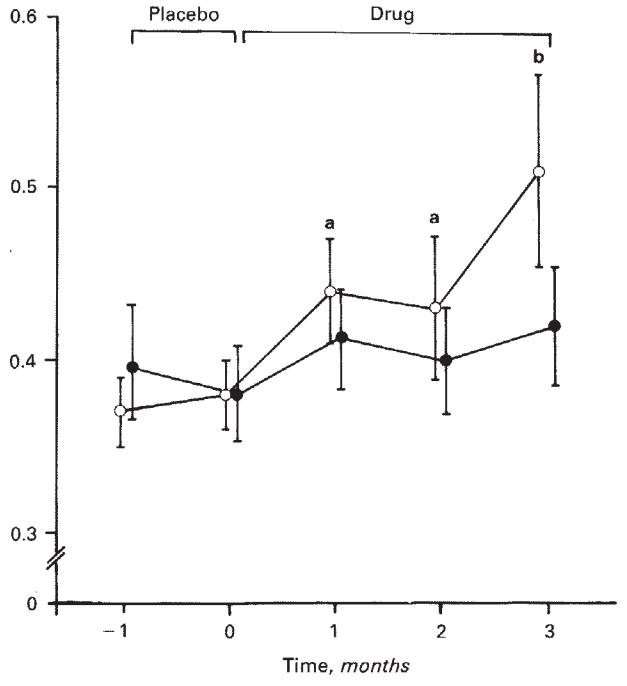

Fig. 5. *The influence of increasing doses of lovastatin (open circles) and simvastatin (solid circles) on the ratio of triglyceride to cholesterol in LDL in HD patients.* Data represent the mean ± SEM from 36 patients. a = $P < 0.05$, b = $P < 0.01$.

but symptoms did not disappear even two months after cessation of therapy making simvastatin-associated side effects unlikely.

Accumulation

In 13 patients of group II plasma could be obtained after three months of treatment with simvastatin (40 mg during the last month) for determination of simvastatin plasma levels (hydroxy-acid form). Measurements were performed 13.4 ± 1.5 hours after the administration of the drug. In five patients values ranged from 4 to 15 ng/ml ten hours after the last dose. One patient demonstrated a value of 45 ng/ml eleven hours after the last dose in the absence of clinical and laboratory side effects. In another six patients values ranged from 4 to 17 ng/ml 12 to 23 hours after the last simvastatin administration.

In a separate investigation, lovastatin and mevalonate determinations were performed in ultrafiltrates of ten hemodialysis patients after administration of a single dose of lovastatin (80 mg) three hours before hemodialysis. An ultrafiltrate sample was obtained within 10 minutes after initiation of hemodialysis. Mean inhibitory concentration in ultrafiltrates (using dialyzers made of polysulfone, F60, Fresenius, Oberursel, Germany) was significantly higher (14.7 ± 2.9 ng/ml) after lovastatin as compared to ultrafiltrates from the same patients taking no lovastatin (3.6 ± 0.5 ng/ml; $P < 0.05$). Mevalonate concentration in ultrafiltrates were also higher after lovastatin (16.6 ± 4.0 ng/ml) as compared to ultrafiltrates from controls (11.8 ± 4.5 ng/ml).

Discussion

The effect of HMG-CoA reductase inhibitors on plasma lipoproteins, lipids and apolipoproteins in hypercholesterolemic HD patients is described. It should be emphasized that screening of 700 HD patients was necessary to select 40 patients displaying hypercholesterolemia associated with mild hypertriglyceridemia. Lovastatin and simvastatin effectively reduced total and LDL cholesterol and increased HDL cholesterol in patients on hemodialysis, so the overall effect of HMG-CoA reductase inhibition on the LDL/HDL ratio appeared favorable. Therefore, the effects of the two HMG-CoA reductase inhibitors on these lipoproteins are in general agreement with those from investigation in nonuremic individuals, where lovastatin and simvastatin have been shown to consistantly lower total and LDL cholesterol [25]. Another remarkable effect of cholesterol synthesis inhibition was the reduction of cholesterol in VLDL. Consequently, the ratio of triglycerides/cholesterol in VLDL increased.

The major dyslipidemia of patients with chronic renal failure is an increase in plasma triglycerides [26, 27]. Generally, triglyceride levels are between 200 and 600 mg/dl, and elevations occur mainly in VLDL, although intermediate density lipoproteins (IDL) may be increased and, also LDL are enriched in triglycerides [reviewed 28]. In this group of HD patients the weight of published evidence also suggests that remnants of triglyceride rich lipoproteins and not LDL are the atherogenic particles [13, 14, 29]. It has been shown that HMG-CoA reductase inhibitors are effective in Type III hyperlipoproteinemia. However, Type III hyperlipoproteinemia and the hyperlipoproteinemia in renal disease are comparable only in that IDL may accumulate. Such IDL in these two patient groups are entirely different in structure with the presence of receptor-defective E2 in type III IDL. Furthermore, in uremic patients apo-C-III is elevated and apo-C-II and E are decreased. Windler, Chao and Havel [30] recently demonstrated that the relative concentrations of the C and E apolipoproteins carried by triglyceride-rich lipoproteins affect remnant removal from plasma. HMG-CoA reductase inhibitors induce the expression of the LDL receptor on liver cells. Therefore, apo B/E rich lipoproteins could effectively be metabolized upon HMG-CoA reductase inhibition. It should be noted that the patients selected in this study were not typical hemodialysis patients in regard to their lipoprotein pattern. They also exhibited elevated levels of LDL and VLDL cholesterol. The underlying methodology did not permit discriminate between IDL and LDL. Lipoproteins exhibiting a hydrated density of less than 1.006 g/ml were floating and the 1.006 infranate contained IDL and LDL. In addition to the marked reduction of LDL cholesterol, also cholesterol content in VLDL was profoundly reduced by lovastatin and simvastatin (Tables 1 and 2). Consequently, the ratio of triglycerides to cholesterol in VLDL normalized, indicating VLDL formation rich in triglycerides and poor in cholesterol. However, it remaines to be proven that HMG-CoA reductase inhibitors influence IDL in this patient type.

The effects of lovastatin and simvastatin on HDL cholesterol were variable. The results are in general agreement with studies in nephrotic syndrome. Two trials with low baseline HDL levels reported increases in HDL cholesterol after HMG-CoA reductase inhibition [31, 32]. Two other trials with normal

baseline HDL levels found little changes after treatment with HMG-CoA reductase inhibitors [33, 34]. The same effect was observed in the present study.

Few adverse effects were seen in the present study. No patient developed a complication necessitating cessation of therapy. It has been demonstrated that the elimination of lovastatin and simvastatin occurs primarily by the liver and dose reduction has not been recommended in renal insufficiency. However, interference with their transport into bile, by either concomitant drug therapy, could raise blood levels and predispose to accumulation and myopathy [18]. Therefore, this group of patients, who were especially prone to muscular damage and side effects, were monitored closely in the present study to detect complications early. On the other hand, it is not known to what extent excess myoglobin released into the circulation does any harm to an individual whithout excretory renal function. Extensive hemodialysis using membrane material with high cut-off rates should overcome excess myoglobin levels sufficiently. Hagemenas, Papu and Illingworth [35] showed that 100 mg of C^{14} simvastatin given in a single dose to healthy subjects was completely cleared from the circulation after 12 hours. In several of our patients inhibitory activity of simvastatin could be detected in plasma even 15 hours after simvastatin administration, and in one patient a marked increased value was observed at 11 hours after simvastatin administration. None of the patients with detectable levels of simvastatin in plasma had evidence for clinical side effects or laboratory abnormalities. Since lovastatin is removed in small quantities in the dialysis fluid, it might help to reduce toxicity. Nevertheless, these data suggest that dose reduction should be recommended for HD patients treated with HMG-CoA reductase inhibitors.

In summary, lovastatin and simvastatin profoundly affect the composition of lipoprotein particles in selected HD patients with hypercholesterolemia and mild hypertriglyceridemia. There is a reduction of the total cholesterol and cholesterol content in VLDL as well as a normalization of the ratio of triglycerides to cholesterol in VLDL. Triglyceride content of the various particles was only affected in some patients treated with simvastatin. In this short term study the two cholesterol synthesis inhibitors had only few side effects and no clinical signs of drug accumulation were observed. It appears that there are only a few selected patients with high serum cholesterol level among all HD patients who could be candidates for this kind of treatment. However, more research is needed to define safe drug dosages for treatment of patients on dialysis.

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References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697–701, 1974
2. Ibels LS, Simans LA, King JO, Williams PF, Neale FC, Stewart JH: Studies on the nature and courses of hyperlipidaemia in uraemia maintenance dialysis and renal transplantation. *Quart J Med* 176:101–106, 1975
3. Scharf S, Wexler J, Longnecker RE, Blaufox MD: Cardiovascular disease in patients on chronic hemodialysis therapy. *Progr Cardiovasc Dis* 22:343–356, 1980
4. Hahn R, Oette K, Mondorf H, Finke K, Sieberth HG: Analysis of cardiovascular risk factors in chronic hemodialysis patients with special attention to the hyperlipoproteinemias. *Atherosclerosis* 48:279–288, 1983
5. Green D, Stonk NJ, Krumlovsky FA: Putative atherogenesis factors in patients with chronic renal failure. *Progr Cardiovasc Dis* 26:133–144, 1983
6. Nicholls AJ, Catto GRD, Edward N, Engeset J, McLeod M: Accelerated atherosclerosis in long-term dialysis and renal-transplant patients: Fact of fiction? *Lancet* i:276–278, 1980
7. Bonomini V, Feletti C, Scolari MP, Stefoni S, Vangelista A: Atherosclerosis in uremia: A longitudinal study. *Am J Clin Nutr* 33:1493–1500, 1980
8. Port FK: Mortality and causes of death in patients with end stage renal failure. *Am J Kidney Dis* 15:215–217, 1990
9. Brunzell JD, Albers JJ, Haas LB, Goldberg AP, Agadoa L, Sherrard DJ: Prevalence of serum lipid abnormalities in chronic hemodialysis. *Metabolism* 26:903–908, 1977
10. Lipid Research Clinics Programm: The Lipid Research Clinics Coronary Prevention Trial Results: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 251:365–374, 1984
11. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Mäenpää H, Mälkönen, Mänttäri M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Nikkilä EA: Helsinki heart study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors and incidence of coronary heart disease. *N Engl J Med* 317:1237–1245, 1987
12. Querfeld U, Ritz E: Atherogenesis—is it accelerated in uremia? *Semin Dial* 2:246–252, 1989
13. Nestel PJ, Fidge NH, Tan MH: Increased lipoprotein-remnant formation in chronic renal failure. *N Engl J Med* 307:329–333, 1982
14. Minamisono T, Wada W, Akamatsu A, Okabe M, Handa Y, Morita T, Asagani C, Naito HD, Nakamoto S, Lewis LA, Mise J: Dyslipoproteinemia, a remnant lipoprotein disease in uremic patients on hemodialysis. *Clin Chim Acta* 84:163–168, 1978
15. Langer T, Levy R: Acute muscular syndrome associated with administration of clofibrate. *N Engl J Med* 279:856–858, 1968
16. Pierides AM, Alvarez-Ude F, Kerr DNS: Clofibrate induced muscle damage in patients with chronic renal failure. *Lancet* ii:1279–1282, 1975
17. Grützmacher P, Scheuermann E-H, Siede W, Lang PD, Abshagen U, Radtke HW, Baldamus CA, Schoeppe W: Lipid lowering treatment with bezafibrate in patients on chronic haemodialysis: Pharmacokinetics and effects. *Klin Wochenschr* 64:910–916, 1986

18. GRUNDY SM: Management of hyperlipidemia of kidney disease. *Kidney Int* 37:847–853, 1990
19. WANNER C, HÖRL WH: Carnitine abnormalities in patients with renal insufficiency: Pathophysiological and therapeutical aspects. *Nephron* 50:89–102, 1988
20. SCHRADER J, STIBBE W, ARMSTRONG VW, KANDT M, MUCHE R, KÖSTERING H, SEIDEL D, SCHELER F: Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. *Kidney Int* 33:890–896, 1988
21. HAMAZAKI T, NAKAZAWA R, TATENO S, SIISHIDO H, ISODA K, HATTORI Y, YOSHIDA T, FUJITA T, YANO S, KUMAGAI A: Effects of fish oil rich in eicosapentaenoic acid on serum lipid in hyperlipidemic hemodialysis patients. *Kidney Int* 26:81–84, 1984
22. GERMERSHAUSEN J, HUNT V, BOSTEDOR R, BAILEY P, KARKAS J, ALBERT A: Tissue selectivity of the cholesterol lowering agents, lovastatin, simvastatin and pravastatin in rats in vivo. *Biochem Biophys Res Commun* 158:667–675, 1989
23. WIELAND H, SEIDEL D: Improved assessment of plasma lipoprotein patterns: IV. Simple preparation of a lyophilized control serum containing intact human plasma lipoproteins. *Clin Chem* 28:1335–1337, 1982
24. MANUAL OF LABORATORY OPERATION: LIPID RESEARCH CLINICS PROGRAM: DHEW No (NIH) 75-628 Bethesda, MD, National Heart and Lung Institute, 1974, pp 1–74.
25. TOBERT JA, HITZENBERGER G, KUKOVETZ WR, HOLMES IB, JONES KH: Rapid and substantial lowering of human serum cholesterol by mevinolin (MK-803), an inhibitor of hydroxymethylglutaryl-coenzyme A reductase. *Atherosclerosis* 41:61–65, 1982
26. BAGDADE JD, PORTE D, BIERMAN EL: Hypertriglyceridemia: A metabolic consequence of chronic renal failure. *N Engl J Med* 279:181–185, 1968
27. ATTMAN P-O, ALAUPOVIC P, GUSTAVSON A: Serum apolipoprotein profile of patients with chronic renal failure. *Kidney Int* 32:368–375, 1987
28. WANNER C, FROMMHERZ, HÖRL WH: Hyperlipidemia in chronic renal failure: Pathophysiological and therapeutical aspects. *Cardiology* (in press)
29. WILSON DE, CHAN I-F, CHEUNG AK, DUTZ W, BUCHI KN: Retinyl ester retention in chronic renal failure: Further evidence for a defect in chylomicron remnant metabolism. *Atherosclerosis* 57: 189–197, 1985
30. WINDLER E, CHAO Y, HAVEL RJ: Determinants of hepatic uptake of triglyceride-rich lipoproteins and their remnants in the rat. *J Biol Chem* 225:5475–5480, 1980
31. VEGA GL, GRUNDY SM: Lovastatin therapy in nephrotic hyperlipidemia: Effects on lipoprotein metabolism. *Kidney Int* 33:1160–1168, 1988
32. RABELINK AJ, HENE RJ, ERKELENS DW, JOLES JA, KOOMANS HA: Effects of simvastatin and cholestyramine on lipoprotein profile in hyperlipidaemia of nephrotic syndrome. *Lancet* ii:1335–1338, 1988.
33. GOLPER TA, ILLINGWORTH DR, NORRIS CD: Lovastatin in the treatment of multifactorial hyperlipidemia associated with proteinuria. *Am J Kidney Dis* 13:312–320, 1989
34. KASISKE BL, VELOSA JA, HALSTENSON CE, LABELLE P, LANGENDÖRFER A, KEANE WF: The effects of lovastatin in hyperlipidemic patients with the nephrotic syndrome. *Am J Kidney Dis* 15:8–15, 1990
35. HAGEMENAS FC, PAPU AS, ILLINGWORTH DR. The effects of simvastatin on plasma lipoproteins and cholesterol homeostasis in patients with heterozygous familial hypercholesterolaemia. *Eur J Clin Invest* 2:150–157, 1990